Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pediatrics and Neonatology (2020) 61, 253–254

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com

Perspectives

Interleukin-6 levels in children developing SARS-CoV-2 infection

Gita Vita Soraya [a,1], Zulvikar Syambani Ulhaq [b,*,1]

[a] *Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, 90245, Indonesia*
[b] *Department of Biochemistry, Faculty of Medicine and Health Sciences, Maulana Malik Ibrahim Islamic State University of Malang, Batu, East Java, 65151, Indonesia*

Received Apr 12, 2020; received in revised form Apr 23, 2020; accepted Apr 29, 2020
Available online 4 May 2020

Since the declaration of the coronavirus disease 2019 (COVID-19) pandemic status, the total number of cases developing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has reached 1,696,588 worldwide, with a mortality rate of 6.24%.[1] Interestingly, reports have shown that, compared to adults, the pediatric populations have lower infection rates, less severe clinical presentation with lower likelihood of progression, and more favorable prognosis.[2] However, the mechanism behind this phenomenon remains elusive. Recently, we demonstrated that COVID-19 severity in adult patients was strongly associated with higher interleukin-6 (IL-6) levels.[3] Thus, in this article, we aimed to evaluate the current evidence regarding IL-6 levels in pediatric COVID-19 cases.

Records, dated up to April 5th, 2020, were identified through electronic databases with search terms such as "COVID-19," "SARS-CoV-2," "IL-6," "pediatrics," "neonates," "infants," "children," and "adolescents." No language restrictions were applied. We synthesized the data from seven studies with a total sample size of n = 127 pediatric patients, with ages ranging from newborn to adolescence.[4–10] Subsequently, one study was excluded[10] due to samples testing negative for SARS-CoV-2 The final sample yielded a size of n = 117, with slightly higher infection rates among males (59.8%), which is consistent with previous reports.[5]

In contrast to our previous result in adults,[3] we observed that pediatric COVID-19 cases had IL-6 levels within normal range (mean: 86.3%; range from 67 to 100%) (Table 1) and that all of the current studies observed patients having mild symptoms. To illustrate, a study with a representative population range of three days to 16 years of age[5] found an overall mild clinical presentation among cases and increased IL-6 levels were only observed in 17.14% of the total population. In line with this finding, the tendency of mild clinical presentation in children has likewise been recognized in a large epidemiologic study of 2163 children in China[11], among which only 0.6% progressed into severe disease.

This finding reinforces previous notions that the cytokine storm, indicated by excessive circulating IL-6, is a possible mechanism of COVID-19 progression[3] and that this aggressive inflammatory cascade is less likely to occur in children. The findings also emphasize that IL-6 better reflects the severity of COVID-19 clinical presentation and is relatively more consistent compared to other inflammatory markers such as C-reactive protein (CRP).[12]

Several factors may contribute to the milder presentation observed in children in regard to the immunopathogenic response. The less mature immune system of children

* Corresponding author.
E-mail address: zulhaq@kedokteran.uin-malang.ac.id (Z.S. Ulhaq).
[1] These authors share first co-authorship to this manuscript.

https://doi.org/10.1016/j.pedneo.2020.04.007

Table 1 Characteristic of included studies.

Characteristics	Zhang et al.[4]	Yu et al.[5]	Du et al.[6]	Sun et al.[7]	Su et al.[8]	Zeng et al.[9]
Location	China	China	China	China	China	China
Number of cases	3	82	14	8	9	1
Age	6—9 years	3 days - 16 years	6.20 (median)	2 mo - 15 years	11 mo - 9 years	2 weeks (neonates)
Males, %	100	62.2	42.9	75	33.3	100
Major clinical feature	Mild	Mild	Mild-intermediate	Mild	Asymptomatic - mild	Mild
IL-6	67% ↔	82.86% ↔	92.85% ↔	75% ↔	100% ↔	↔

↔ value within the normal reference range.

may result in the lower capability to elicit cytokine release against viral infection, relative to the more mature and vigorous immune responses observed in adults. Other possible explanations include healthier respiratory tracts and less pre-existing damage in children compared to adults.

There are several limitations identified in this current analysis. Only a few studies reported the IL-6 level in COVID-19-infected pediatric patient, with some variations on the IL-6 reference ranges between studies. Thus, further studies with larger sample size and homogenous or standardized measurement are needed to confirm these findings. Additionally, more studies need to focus on the neonate age group, as data regarding clinical presentation of COVID-19 in this highly susceptible age group remains scant. In summary, these findings confirm that IL-6 reflect presence of marked inflammation and severe COVID-19. Based on current evidence, IL-6 levels of children with SARS-CoV-2 infection tend to be within normal range, which reflects the mild nature of clinical presentation in the pediatric population.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None to declare.

References

1. WHO. *Coronavirus disease 2019 (COVID-19) situation report — 83*. WHO; 2020. Available at https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200412-sitrep-83-covid-19.pdf?sfvrsn=697ce98d_4. Accessed April 12, 2020.
2. Hong H, Wang Y, Chung HT, Chen CJ. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. *Pediatr Neonatol* 2020;**61**:131—2.
3. Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. *Med Mal Infect* 2020;**50**:382—3.
4. Zhang T, Cui X, Zhao X, Wang J, Zheng J, Zheng G, et al. Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia. *J Med Virol* 2020. https://doi.org/10.1002/jmv.25795.
5. Yu H, Cai Q, Dai X, Liu X, Sun H. The clinical and epidemiological features and hints of 82 confirmed COVID-19 pediatric cases aged 0-16 in Wuhan, China. *MedRxiv* 2020. https://doi.org/10.1101/2020.03.15.20036319.
6. Du W, Yu J, Wang H, Zhang X, Zhang S, Li Q, et al. Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China. *Infection* 2020. https://doi.org/10.1007/s15010-020-01427-2.
7. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr* 2020. https://doi.org/10.1007/s12519-020-00354-4.
8. Su L, Ma X, Yu H, Zhang Z, Bian P, Han Y, et al. The different clinical characteristics of corona virus disease cases between children and their families in China - the character of children with COVID-19. *Emerg Microbes Infect* 2020;**9**:707—13.
9. Zeng LK, Tao XW, Yuan WH, Wang J, Liu X, Liu ZS. First case of neonate infected with novel coronavirus pneumonia in China. *Zhonghua Er Ke Za Zhi* 2020;**58**:E009 [Article in Chinese].
10. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020;**9**:51—60.
11. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020. https://doi.org/10.1542/peds.2020-0702.
12. Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. *Clin Chem Lab Med* 2020. https://doi.org/10.1515/cclm-2020-0272.